REMARKS

Claims 13-21, 23-25, 27, 28 and 31 are pending in the application. Claims 13-20 have been withdrawn from further consideration as being drawn to non-elected inventions. In a desire to advance prosecution of this case and without admitting the propriety of the rejections, Applicants provide herein an amended claim set for the Examiner's consideration. Applicants respectfully request consideration of the following remarks with respect to the outstanding rejections.

Rejections Under 35 U.S.C. § 112, first paragraph: Enablement

Claims 21, 23-25, 27, 28, and 31 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Applicants respectfully traverse.

Claim 21 has been amended consistent with the descriptions in the specification, for example on page 9 (lines 15-19) and pages 11-13. Applicants respectfully submit that the scope of enablement is commensurate with the scope of the claims. Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejections Under 35 U.S.C. § 112, first paragraph: Written description

Claims 21, 23-25, 27, 28 and 31 stand rejected under 35 U.S.C. § 112, first paragraph for lack of written description. Applicants respectfully traverse.

Applicants submit that the amendments described above are consistent with the disclosure in the specification and also resolve any issues of written description. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph for lack of written description.

Rejections Under 35 U.S.C. § 112, second paragraph: Indefiniteness

Claims 21, 23-35, 27, 28 and 31 stand rejected under 35 U.S.C. § 112, second paragraph because claim 21 is suggested as lacking a positive process step relating to the preamble of the claims. Applicants respectfully traverse.

The method of Claim 21 comprises contacting at least one T cell of said host with a self antigen preparation and a CTLA-4 blocking agent, wherein the contacting is effective to break immune tolerance against the self antigen. A result of the process is subsequent increase in activation of autoreactive T cells against non-T cell tumor cells and normal tissue

cells displaying the self-antigen. In other words, increasing activation of T cells against non-T cell tumor cells and tissue cells simply states the results of the claimed process. As such, all positive steps delimiting the method is properly presented in claim 21. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 21, 23-25, 27, 28 and 31 stand rejected under 35 USC § 112, second paragraph because the phrase "characterized as specifically binding to the extracellular domain of CTLA-4 and inhibitory of CTLA-4 signaling" is suggested as being indefinite. Applicants respectfully traverse.

Applicants reassert that the phrase is properly interpreted in view of the specification as requiring that the claimed blocking agent: 1) specifically binds to the extracellular domain of CTLA-4 and 2) inhibits CTLA-4 signaling. (See, e.g., page 8, line 7 through page 9, line 31). As discussed previously, these functional characteristics are readily assayed using various art-recognized methods, for example as described in the specification on pages 8-15 and exemplified by the Examples. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 102: Anticipation

Claims 21, 23, and 27 stand rejected under 35 USC § 102(a) as being anticipated by Leach et al., *Science* 271:1734-1736 (1996). The Examiner suggests that Leach inherently teaches the claimed methods. Applicants respectfully traverse.

Leach teaches inhibiting tumor cell growth by administering CTLA-4 blocking agent to animals injected with 51BLim10 tumor cells, a transplantable murine colon carcinoma cell line propagated in cell culture, or SalN tumor cells, a fibrosarcoma of A/JCr mice. The Office Action, however, does not identify within Leach whether the two cell lines express a self antigen expressed on tissue cells from which the tumor arose and whether injection of the tumor cell line is sufficient to break immune tolerance against such self-antigens.

In contrast, claim 21 provides for contacting a T cell with a preparation comprising a CTLA-4 blocking agent and a self-antigen expressed on tissue cells and non-T cell tumors cells arising from such tissue. Importantly, the contacting must be sufficient to break immune tolerance against the self antigen. The result is an increase in activation of autoreactive T cells against both the tumor cells and tissue cells expressing the self antigen. Example 1 shows this effect in the depigmentation of skin and hair as a result of immune mediated destruction of normal pigment containing cells following administration of CTLA-4

blocking agent subsequent to injection of B16-BL6 tumor cells into the animals. Example 2 further demonstrates this activation of autoreactive T-cells in a different tissue, the prostate. Treatment with anti-CTLA-4 antibodies and irradiated prostate tumor cells containing a transgene expressing GM-CSF causes prostatitis in the animal. Thus in Examples 1 and 2, there is concrete evidence of increased activation of autoreactive T cell response against normal tissue cells in addition to a response against tumor cells arising from the tissue.

For a rejection based on anticipation, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See Verdegaal Bros. v. Union Oil of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). If the rejection rests on inherency of a claimed limitation, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency of the result or characteristic." See M.P.E.P. § 2112; see also In re Rijckaert, 28 USPQ2d 1955 (Fed. Cir. 1993) (reversing rejection because inherency was based on what would result from optimization of conditions, not necessarily present in the prior art). The guidelines further provide

> To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and *that it would be so recognized by persons of ordinary skill in the art.* Inherency, however, cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

See M.P.E.P. § 2112 (emphasis added). In the context of method claims, even if the claimed method comprises steps identical to those of the method practiced in the prior art, the accidental or unwitting achievement of that result cannot constitute anticipation. See In re Marshall, 198 USPQ 344, 346 (CCPA 1978).

Leach teaches injecting a carcinoma cell line 51BLim10 or SalN fibrosarcoma into mice and administering a CTLA-4 blocking agent to inhibit growth of the tumor cells in the animal. However, objective evidence in Leach is not pointed out by the Examiner to (1) show that carcinoma cell line 51BLim10 or SalN fibrosarcoma expresses a self antigen expressed on the tissue from which the tumor cells arose, (2) indicate that contact with 51Blim10 or SalN cells was sufficient break immune tolerance against a self-antigen expressed on normal tissue, and (3) proffer any evidence of recognition in the references that the claimed result, increase activation of autoreactive T cells against both tissue cells and non T cell tumor cells from which the tumor arose, necessarily follows from the process in Leach.

For example, the Office Action provides no results in Leach of an immune reaction against colon tissue in the subject animal which might indicate breaking of immune tolerance against a self antigen. The applied technical reasoning in the Office action, reiterating claim language that tumor vaccine is a self antigen preparation sufficient to produce the recited results, is merely conclusory:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reason to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

See M.P.E.P. § 2112. Extrinsic evidence has not been set forth to demonstrate with the required level of certainty (i.e., necessarily) the existence of the claimed self antigen and that breaking of immune tolerance against any such self antigen occurs from use of 51Blim10 colon carcinoma or SalN fibrosarcoma cell lines.

The Examiner cites the case of Ex parte Novitski, 26 USPQ2d 1389 (BPAI 1993) as relevant legal support for the rejection. The claims in Novitski dealt with a method for protecting a plant from pathogenic nematodes by inoculating the plant with nematode inhibiting *Pseudomonas cepacia*, a bacterial strain which had been described in the prior art for use on plants as an antifungal agent. See id. at 1390. Although the prior art did not expressly disclose its use as an anti-nematicidal agent, the Board found the claims anticipated based on inherency. This decision, however, rested on the applicant's disclosure indicating *knowledge* of the bacterial strain's nematode inhibiting properties:

> In this regard, note particularly appellant's disclosure in the instant specification, page 18, that *Pseudomonas cepacia* type Wisconsin 526 possesses an 18% nematode-inhibition rating.

See id. at 1390. Further, the Board emphasized applicant's own *admission* in a reply brief that the bacterial strain possessed an inherent nematicidal activity. See id. 1391. Thus, the holding in Novitski is confined to the specific facts of the case and is inapposite to the present claims.

A more appropriate case is In re Zierden, 162 USPQ 102 (CCPA 1969). One claim at issue in Zierden was directed to a method for removing alluvium deposits in industrial waters using insoluable sodium metaphosphate and a solubilizing agent. The examiner rejected the claim over a French patent, which disclosed use of the same composition to remove scale from industrial waters. The court reversed and held that the French patent provided no

teaching of removal of alluvium from industrial waters. The court reasoned that not all industrial waters contained alluvium, particularly since it was known in the prior art that some industrial waters were filtered to remove alluvium prior to treatment with the sodium metaphosphate compound. Consequently, practice of the method in the French patent did not *necessarily* result in the claimed process.

Another case of particular relevance to inherency issues in this application is the holding in Glaxo, Inc. v. Novopharm Ltd., 34 USPQ2d 1565 (1995). In Glaxo, the claim at issue was directed to a particular crystalline form (Form 2) of rantidine (i.e., "Zantac"), which had advantageous filtering and drying properties. The prior art asserted against the claim disclosed a method of making rantidine. Although the accused infringer conclusively showed that the prior art process produced Form 2 in addition to another form of the drug, the Federal Circuit upheld the district court's ruling that the prior art patent did not inherently anticipate the claim since the known process could yield either type of rantidine polymorphs and did not always result in producing Form 2. See id. at 1567.

In view of the foregoing, sufficient objective evidence has not been set forth to show that Leach expressly or inherently discloses every limitation in the claims. Accordingly, Applicants respectfully request withdrawal of the rejection under § 102(a) over Leach.

Claims 21, 23-25, 27 and 28 stand rejected under 35 U.S.C. § 102(e) as anticipated by Allison et al., U.S. Patent No. 5,811,097 ('097) or Allison et al., U.S. Patent No. 5,855,887 ('887). The Office Action asserts that a tumor vaccine of tumor cells or tumor cell lysates "will" contain "tumor associated self antigens," and thus result in growth inhibition of tumor cells. Applicants respectfully traverse.

Applicants address '097 and '887 patents together since they have similar descriptions of CTLA-4 blockade for inhibiting tumor cell growth. Both patents disclose growth inhibition of carcinoma cell line 51BLim10 as essentially described in Leach (see, e.g., patent '887, Example 2). The cited references also suggest use of tumor antigens, in the form of purified proteins or tumor cell lysates, in combination with CTLA-blockade, and lists a number of specific tumor antigens (see, e.g., patent '887, column 9, lines 15-35).

Because the previous discussion sufficiently addresses issues arising from studies involving 51Blim10 cell line, the following discussion of these references is directed to use of tumor vaccines composed of tumor cells or tumor cell lysates. The Office Action argues for the inherent presence of tumor-associated self antigens in tumor vaccines of tumor cells and tumor cell lysates. The present claims, however, recite use of a preparation containing

self antigen expressed on tissues from which the non-T cell tumor arose. Importantly, contact with the combination of CTLA-4 blocking agent and the self antigen must act to break immune tolerance against the self antigen, thereby eliciting an increase in autoreactive T cell response against both the tumor cells and normal tissue cells.

On the other hand, the Office Action has not pointed out objective evidence in patents '097 and '887, or proffered extrinsic evidence to show that tumor cell lysates necessarily contain a self antigen present on a tissue from which the tumor cells arose. Further, objective evidence is lacking to demonstrate any recognition by those skilled in the art at the filing date of the patents '097 and '887 that contacting T cells with CTLA-4 blocking agent and tumor cells or tumor cell lysates would be sufficient to break tolerance to a specified self antigen and result in destruction of normal tissue cells.

In view of the foregoing, the required showing that the claimed limitations "necessarily flows" from use of tumor cells and tumor cell lysates has not been met. As given above, the unwitting accomplishment of the recited limitations is not proper basis to reject claims via inherency. Accordingly, Applicants respectfully request withdrawal of the rejections under § 102(e) over U.S Patent Nos. 5,811,097 or 5,855,887.

Rejections Under 35 U.S.C. 103(a): Obviousness

Claims 21, 23-25, 27, 28 and 31 stand rejected under 35 U.S.C. § 103(a) as obvious over Leach et al., *Science* 271:1734-1736 (1996) in view of Heslop, *Baillieres Clinical Haematology* 7:135-151 (1994) (hereinafter Heslop), further in view of Sussman et al., *Annals of Surgical Oncology* 1:296-306 (1994) (hereinafter Sussman) and further in view of Wallack et al., *Mt Sinai J. Med.* 59:227-233 (1992) (hereinafter Wallack). The current Office Action reiterates the reasons enumerated in prior Office Action mailed May 22, 2001 (Paper No. 12). Applicants respectfully traverse.

Leach and its contents have been discussed above.

Heslop teaches introduction of cytokine genes into tumor cells or immune system effector cells and subsequent transfer of these cells into afflicted patients to increase levels of cytokines at tumor sites, thereby activating immune response against tumor cells.

Sussman teaches adoptive immunotherapy in which immune system cells (i.e., lymphocytes) obtained from patients are stimulated *ex vivo* and reintroduced into the patient to inhibit tumor cell growth. Sussman characterizes this approach as passive immunotherapy. The *ex vivo* treatments include (1) exposure to lymphokine IL-2, (2) activation in presence of

immunoadjuvant *C. parvum* and IL-2, (3) activation in presence of bacterial adjuvant BCG and irradiated tumor cells, and (4) use of monoclonal antibody directed against CD3 complex in combination with IL-2.

Wallack discloses various experimental and clinical trials for treating cancer using oncolysates generated from virus infected tumor cells. The oncolysates can elicit immune responses against the tumor cells when injected into an animal bearing the tumor. In particular, the reference describes use of vaccinia virus to infect melanoma cells to generate melanoma viral oncolysates. Although it appears to Applicants that the previous Office Action suggested that Wallack teaches use of tumor cell lysates in the presence of GM-CSF to inhibit tumor cell growth (see ¶ 16), Applicants are unable to find reference to use of GM-CSF or any other cytokine in Wallack. Clarification is respectfully requested.

In rejecting claims for obviousness under 35 U.S.C. § 103(a), the Examiner bears the burden of establishing a *prima facie* case of obviousness. See In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993); see also M.P.E.P § 2142. To establish a *prima facie* case of obviousness, three criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill in the art with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); see also M.P.E.P. § 706.02(j). If any one these criteria are not met, *prima facie* obviousness is not established.

Leach teaches injection of colon carcinoma cells into mice and administration of CTLA-4 blocking agent to inhibit growth of the tumor cell in the animal. However, as discussed above, the Office Action has not pointed out any teaching or suggestion in Leach, either expressly or inherently, directed to contacting a T cell with a preparation containing a self antigen. Furthermore, objective evidence of prior art recognition that administering a tumor cell or tumor cell lysate to an animal in conjunction with CTLA-4 blockade necessarily - with certainty - results in breaking of immune tolerance against a self antigen expressed on non T cell tumor cells and tissue cells has not been established. The Office Action has not set forth adequate evidence of an autoimmune reaction against the tissue cells from which the non T cell tumor cells arose in the studies of Leach. Heslop, Sussman, and Wallack fail to

provide the necessary teaching or suggestion to cure the defects in Leach. First, the secondary references provide no teaching or suggestion to use CTLA-4 blockade in conjunction with a self antigen preparation to break immune tolerance against the self antigen. Second, the references provide no teaching or suggestion for increasing activation of autoreative T cell against both normal tissue cells and non-T cell tumor cells arising from the subject tissue. On the whole, Leach in view of Heslop, Sussman, and Wallack, either individually or in combination, fail to teach or suggest every limitation of the claimed invention.

Moreover, the M.P.E.P § 2143.01 provides that the presence of individual claim elements in various references is not sufficient to establish *prima facie* obviousness:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.

In the present case, the explanation in the Office Action for sustaining the rejection of claims directed to use of cytokine transduced tumor cells is the teachings of Heslop, which makes no mention of using CTLA-4 blocking agents. Leach, in turn, is directed to use of CTLA-4 blocking agent and demonstration of its ability to inhibit tumor growth. Neither reference, however, teaches or suggests the desirability or advantages of using CTLA-4 blocking agent in combination with cytokine transduced tumor cells containing a self antigen to break immune tolerance against the self-antigen. In particular, the references do not indicate any recognition by the skilled artisan of increased autoreactive immune response against both tissue cells and non-T cell tumor cells.

The Office Action descriptions of the advantages of using cytokine gene transduced tumor cells to inhibit tumor cell growth is a reiteration of the advantages of Heslop, which does not amount to a suggestion or motivation to use a combination of cytokine transduced cells with CTLA-4 blocking agent. In this regard, the Federal Circuit has suggested care from falling into hindsight reconstruction, whereby applicant's disclosure is used to piece together isolated teachings of the prior art to render the claimed invention obvious. See In re Fritch, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

Similarly, the explanation in the Office Action for sustaining the rejection of claims directed to *ex vivo* treatment of T cells refers to the teachings of Sussman, which makes no suggestion of CTLA-4 blocking agents. Leach describes administration of CTLA-4 *in vivo* for inhibiting tumor cell growth.. The two references in combination provide no teaching or

suggestion of the desirability or advantages of using CTLA-4 blocking agent in combination with a self antigen *ex vivo* to break immune tolerance against the self-antigens. The Office Action descriptions of the advantages of *ex vivo* treatment is a reiteration of the advantages of Sussman, which does not amount to a suggestion or motivation to treat T cells *ex vivo* with a combination of self antigen and CTLA-4 blocking agent.

Moreover, Applicants submit that it is unobvious to induce an autoimmune reaction resulting in potential systemic killing of both healthy tissue cells and tumor cells originating from the subject tissue. Conventional medical approaches teach away from eliciting an autoreactive T cell response against healthy, normal tissue cells. The present application, however, expressly describes the advantages of this unconventional therapeutic approach:

> This immunological therapy will find particular use with tumors such as melanoma, mammary cancer, testicular cancer, ovarian cancer, prostate cancer and the like *where loss or modification of some or all of the normal tissue is acceptable, or even desirable, side effect.* In an alternative embodiment, the subject treatment may be used to enhance or effect antigen ablatement of a selected tissue, as a prophylactic measure against cancer development or for other medical reasons.

(See Specification on page 20, line 29 through page 21, line 4) (emphasis added). Further, provided on page 66, lines 16-18:

> As demonstrated herein, the CTLA-4 blockade of the present invention provides an effective immunological treatment of tumors arising from non-essential tissues.

In view of the foregoing, Applicants submit that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a) over Leach in view of Heslop, Sussman, and Wallack.

Claims 21, 23-25, 27-29 and 31 stand rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,811,097 ('097). Claims 21-25, 27-29, and 31 also stand rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,855,887 ('887). Applicants respectfully traverse.

As above, Applicants address the cited references together since the disclosure contents are related, and the basis of rejections are similar, if not identical, for the two references. Justifications for the rejection in the Office Action mailed May 22, 2001 (Paper No. 12), which are reiterated in the current action, discusses at one point the use of "dead or dying tumor cells." (See ¶ 17). However, the asserted claims in Applicants' prior reply has

no indication for use of those particular cells. Additionally, the Examiner's discussion in Paper 12 at ¶ 17 also relates to contacting mammalian T cells with a "second immune response stimulating agent composed of GM-CSF." However, the prior claims refer to cytokine transduced tumor cells. There is some ambiguity as to whether the rejection refers to use of GM-CSF alone or use of transduced tumor cells expressing GM-CSF, where GM-CSF is a representative cytokine. Applicants respectfully request further clarification on this matter.

In regards to the remaining substance of the rejections, Applicants have fully addressed the issue of inherency raised by the Office Action. To recapitulate, no objective evidence nor art recognition has been identified showing that tumor cell lysates *necessarily* contain a self antigen expressed in tissues from which the non-T cell tumor cells arose, or that contacting of T cells with tumor cell lysates and CTLA-4 blocking agent would be sufficient to break immune tolerance against such self antigen and result in an autoreactive T cell response against tissue cells and non-T cell tumor cells expressing the self antigen. In view of the absence of any teaching or suggestion of the missing claim elements, the cited references fail to satisfy the legal criteria for establishing a *prima facie* case of obviousness for independent claim 21. As dependent claims 23-25, 27-29 and 31 ultimately depend from claim 21, these claims are not rendered obvious for at least the same reasons. Accordingly, Applicants respectfully request withdrawal of the rejections under § 103(a) over U.S Patent No. 5,811,097 or U.S. Patent No. 5,855,887.

Double Patenting

Claims 21, 22-25, 27 and 28 stand rejected under judicially created doctrine of obviousness-type double patenting over claims 1,3,4,6,8,18 and 20 of US Patent No 6,051,227. Claims 21, 22-25, 27, 28, and 31 stand rejected under judicially created doctrine of obviousness type double patenting over claims 1, 3, 4, 6, 8, 18 and 20 of U.S. Patent No. 6,061,227 in view of Heslop, *Baillieres Clinical Haematology* 7:135-151 (1994). Claims 21, 23, 25, 27 and 31 stand rejected under judicially created doctrine of obviousness-type double patenting over claims 1 and 6-11 of U.S. Patent No. 5,811,097. Claims 21, 23-25, 27, and 31 stand rejected under judicially created doctrine of obviousness-type double patenting over claims 1, and 6-11 of U.S. Patent No. 5,811,097 in view of Heslop.

Applicants respectfully request that these issues be held in abeyance until a determination of otherwise allowable subject matter is made in the instant case.

CONCLUSIONS

Applicants submit that the claims are in condition for allowance and an early notification of such is solicited. If the Examiner believes that there are further unresolved issues which would benefit from a telephone interview, the Examiner is encouraged to call the undersigned at (415) 781-1989.

Respectfully submitted,
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Dated: 6/5/03

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Filed under 37 C.F.R. § 1.34(a)

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